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Easy to remember, difficult to forget: The development of fear regulation

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ABSTRACT

Fear extinction learning is a highly adaptive process that involves the integrity of frontolimbic circuitry. Its disruption has been associated with emotional dysregulation in stress and anxiety disorders. In this article we consider how age, genetics and experiences shape our capacity to regulate fear in cross-species studies. Evidence for adolescent-specific diminished fear extinction learning is presented in the context of immature frontolimbic circuitry. We also present evidence for less neural plasticity in fear regulation as a function of early-life stress and by genotype, focusing on the common brain derived neurotrophin factor (BDNF) Val66Met polymorphism. Finally, we discuss this work in the context of exposure-based behavioral therapies for the treatment of anxiety and stress disorders that are based on principles of fear extinction. We conclude by speculating on how such therapies may be optimized for the individual based on the patient's age, genetic profile and personal history to move from standard treatment of care to personalized and precision medicine.

1. Introduction

Learning the relationship between threatening events and the cues that predict the onset of those events is an adaptive process that allows an individual to anticipate and minimize exposure to danger (Ohman and Mineka, 2001). Failure to regulate fear expression in response to a cue that no longer predicts imminent threat can lead to chronic fear expression and sustained periods of heightened anxiety. This can set the stage for the emergence of stress and anxiety-related disorders.

Research studies that explore fear regulatory processes and the role they play in the etiology of anxiety and stress-related disorders are important because the personal and societal costs of these disorders are immense. Anxiety disorders affect about 40 million American adults in a given year (Kessler et al., 2005), creating significant negative impact on quality of life for victims, as well as an enormous economic burden of more than $35 billion spent annually on treatment and indirect costs of over $4 billion per year in lost productivity (Greenberg et al., 1999). The most common evidence-based behavioral treatment of anxiety disorders is cognitive behavioral therapy (CBT) (Rothbaum and Davis, 2003). Exposure-based CBT is based on principles of fear extinction learning and involves identification of what triggers the anxiety followed by systematic desensitization (repeated exposure) to that trigger in the absence of any threat (Myers and Davis, 2002; LeDoux, 2000). Unfortunately only a little over 50% of individuals with anxiety respond to this therapy (Walkup et al., 2008).

Identifying possible causes for why some individuals are responsive to CBT and others are not is important for guiding personalized treatments (i.e., precision medicine). Whether a given individual benefits from exposure therapy may vary based on extinction learning capacity that is mediated by age, genetic profile and personal history. In

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this article, we provide a brief overview of the literature on fear extinction learning and the underlying neurocircuitry based on human and rodent studies. We examine how acquisition of fear memories and their extinction change across development in humans and rodents, focusing specifically on adolescence when anxiety disorders peak. We then examine genetic and environmental factors that contribute to individual differences in fear regulation and extinction. We conclude by discussing important implications of these findings for whom, when and what type of CBT may be most effective for a patient and suggest novel therapeutic approaches.

2. Neural circuitry underlying the regulation of fear

Fear learning is an adaptive process that allows an organism to respond appropriately to cues or contexts that predict danger. Behavioral paradigms based on the principles of classical conditioning have become the *de facto* standard for studying fear learning in animals and humans. Classical conditioning is a process based on Pavlovian learning principles in which a neutral stimulus is paired with a salient stimulus (Pavlov and Anrep, 1927). During fear conditioning, a conditioned stimulus (the cue) is repeatedly paired with an aversive event (the unconditioned stimulus), such that the presentation of the cue alone comes to elicit a fear response, indicating the acquisition of a conditioned fear response (LeDoux, 2003). Once an associative link between the cue and aversive stimulus is formed and consolidated, it becomes a stable long-term memory.

After a cue is no longer predictive of the onset of danger, however, it is maladaptive to respond as if it is still a threat. Typically a conditioned fear response can be reduced by extinction. During extinction, the cue is repeatedly presented by itself and fear expression decreases, as the animal learns that it no longer reliably predicts the aversive stimulus (Mackintosh, 1974). Early models of fear extinction learning posited that extinction involved the unlearning of associations between a cue and an aversive stimulus (Rescorla and Wagner, 1972). However, it is now accepted that extinction reflects learning of a new memory trace that now competes with the original fear memory for expression (Bouton, 2004; Myers and Davis, 2002). If the extinction memory is strong enough and can be successfully retrieved, fear expression can be suppressed. Substantial evidence shows, however, that while extinction learning can reduce the expression of conditioned fear, extinguished fear may return under a number of different circumstances including the simple passage of time (spontaneous recovery), exposure to an aversive stimulus or stressor (reinstatement) or exposure to a threat cue in a novel context (renewal) (Bouton, 2004; Myers and Davis, 2002). In adaptive terms, this computes logically as the predictive value of an extinguished threat cue might become ambiguous under these conditions, and the penalty for failure to appropriately respond to a threat cue could be injury or death. The return of extinguished fear is therefore not categorically maladaptive. However, when fear regulatory capacity is diminished an individual may respond repeatedly to cues once predictive of danger, even though danger is no longer present. Persistent fear responding to a safety cue is maladaptive and can lead to pathological states of anxiety.

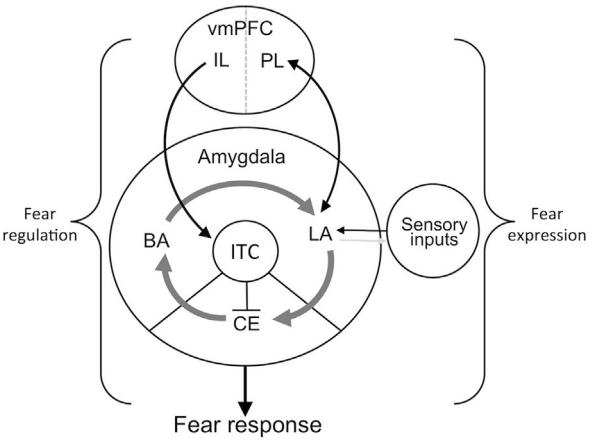

Fig. 1. Fear circuitry. A simplified diagram of the neural circuitry underlying fear expression and regulation. *Abbreviations*: IL, infralimbic prefrontal cortex; PL, prelimbic prefrontal cortex; BA, basal amygdala; LA, lateral amygdala; CE, central amygdala; ITC, intercalated cells; vmPFC, ventromedial prefrontal cortex.

Substantial research in animals and humans has characterized the neural mechanisms underlying fear acquisition and fear extinction learning (Fig. 1). The amygdala, a structure in the medial temporal lobe, is functionally segregated into subnuclei that play distinct roles in fear acquisition and expression (LeDoux, 2007). During fear learning sensory thalamic inputs converge on the lateral amygdala (LA) (Quirk et al., 1995; Collins and Pare, 2000) driving fear expression through the central nucleus (CE) of the amygdala downstream toward output systems that mediate autonomic responses (Maren, 2001). Learning has occurred when the conditioned stimulus alone is able to initiate activity in the LA and elicit a fear response, which prior to conditioning would have been elicited only by the unconditioned stimulus.

The ventral medial prefrontal cortex (vmPFC) is critical for mediating fear expression and extinction (Quirk and Mueller, 2008; Phelps et al., 2004). Two distinct subregions of the rodent vmPFC, the prelimbic and infralimbic cortices, play specific functional roles in the expression and inhibition of fear, respectively (Santini et al., 2008; Sierra-Mercado et al., 2011; Sotres-Bayon and Quirk, 2010). The prelimbic cortex (PL) has been implicated in the expression of fear via bilateral projections to and from the amygdala (Milad and Quirk, 2012). The PL receives transient inputs signaling the presence of threat from the amygdala and transforms these signals into sustained firing via downward projections to the CE (Sotres-Bayon and Quirk, 2010) and toward output systems that generate fear responses. The infralimbic cortex (IL) plays a contrasting role in the storage and recall of extinction memory (Quirk and Mueller, 2008). The LA and basal nucleus (BA) of the amygdala excite cells in the IL in response to safety signals (Repa et al., 2001). Cells in the IL then modulate fear expression through projections to inhibitory (intercalated) cells in the amygdala, that in turn block activity in the